



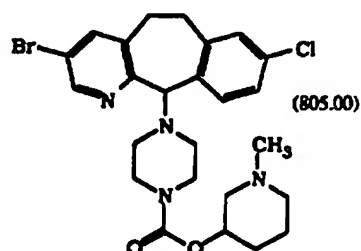
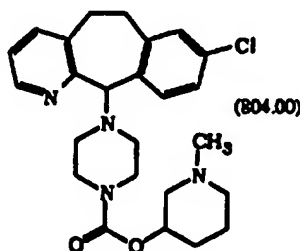
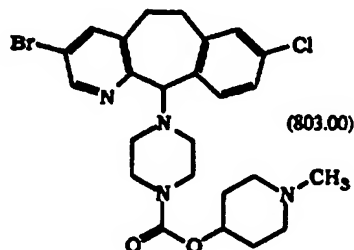
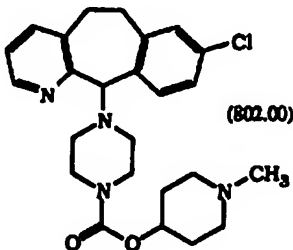
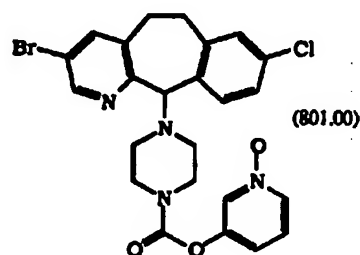
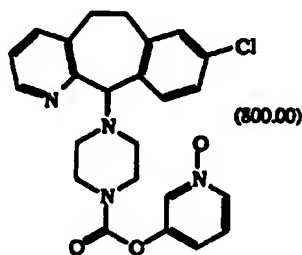
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/495		A1	(11) International Publication Number: WO 96/30018
			(43) International Publication Date: 3 October 1996 (03.10.96)
(21) International Application Number: PCT/US96/03312		(74) Agents: JEANETTE, Henry, C. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).	
(22) International Filing Date: 21 March 1996 (21.03.96)			
(30) Priority Data: 08/410,479 24 March 1995 (24.03.95) US		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).			
(72) Inventors: BISHOP, W., Robert; 17 Hopper Avenue, Pompton Plains, NJ 07444 (US). DOLL, Ronald, J.; 126 Union Avenue, Maplewood, NJ 07040 (US). MALLAMS, Alan, K.; 147 Kings Highway, Hackettstown, NJ 07840 (US). NJORGE, F., George; 2597 Juliat Place, Union, NJ 07083 (US). PETRIN, Joanne, M.; 27 Anderson Parkway, Cedar Grove, NJ 07009 (US). PIWINSKI, John, J.; 6 Saddle Ridge Drive, Lebanon, Clinton Township, NJ 08833 (US). WOLIN, Ronald, L.; 406 Mountain Avenue, Westfield, NJ 07090 (US). TAVERAS, Arthur, G.; 43 Crestwood Road, Rockaway, NJ 07866 (US). REMISZEWSKI, Stacy, W.; 147 Honeysuckle Drive, Township of Washington, Westwood P.O., NJ 07675 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

(54) Title: TRICYCLIC CARBAMATE COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract

A method of inhibiting Ras function and therefore inhibiting cellular growth is disclosed. The method comprises the administration of a compound selected from (800.00), (801.00), (802.00), (803.00), (804.00), or (805.00). Compounds of structures (800.00) - (805.00) are novel compounds.



FOR THE PURPOSES OF INFORMATION ONLY

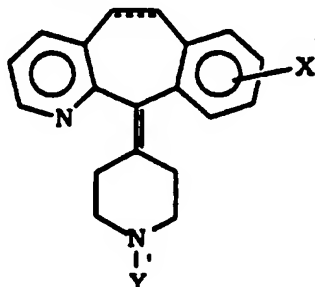
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**TRICYCLIC CARBAMATE COMPOUNDS USEFUL FOR
INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT
OF PROLIFERATIVE DISEASES**

BACKGROUND

International Publication Number WO92/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:



wherein Y' is hydrogen, substituted carboxylate or substituted sulfonyl. For example, Y' can be, amongst others, -COOR' wherein R' is C1 to C6 alkyl or substituted alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl or -2, -3, or -4 piperidyl or N-substituted piperidyl. Y' can also be, amongst others, SO₂R' wherein R' is C1 to C6 alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl. Examples of such potentiating agents include 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines such as Loratadine.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

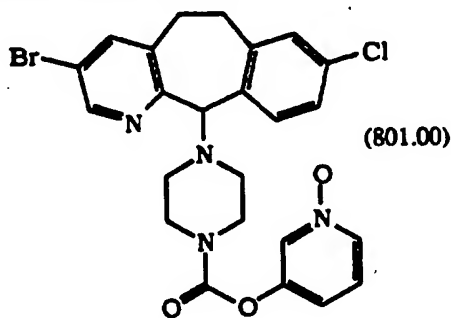
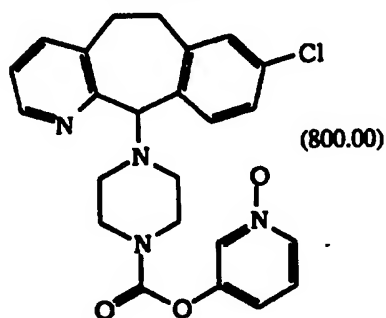
A welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

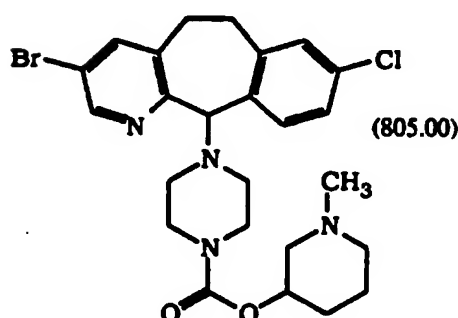
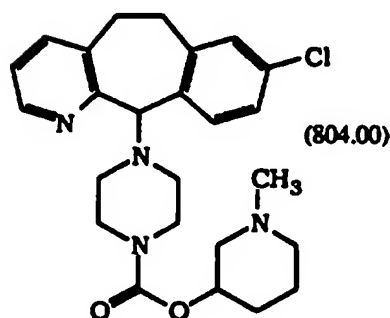
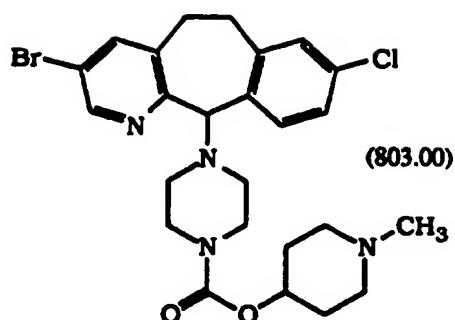
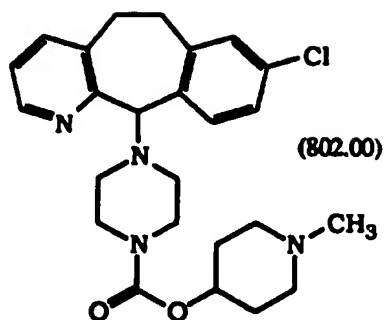
SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, *in vitro*; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

The novel compounds of this invention are:





, and

- 5 These compounds are used in the methods of this invention. Preferred compounds useful in this invention are represented by Formulas 801.00, 802.00, 803.00, 804.00 and 805.00.

- 10 This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g.,
- 15 lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, bladder carcinoma, and
- 20 myelodysplastic syndrome (MDS).

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--

with said inhibition being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, lyn, fyn), may be inhibited by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

The tricyclic compounds useful in the methods of this invention inhibit abnormal cellular growth. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, EtOH and the like are equivalent to the unsolvated forms for purposes of the invention.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric,

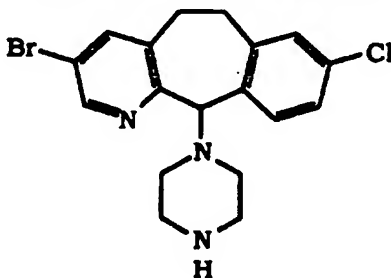
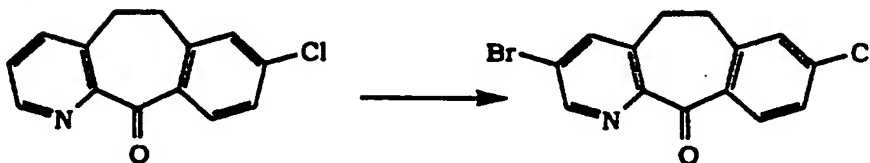
phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds 800.00 to 805.00 may be made by the methods described in WO 95/10515, published April 20, 1995 (e.g. see the preparations described for Formula 400.00), and by the methods described in the examples below.

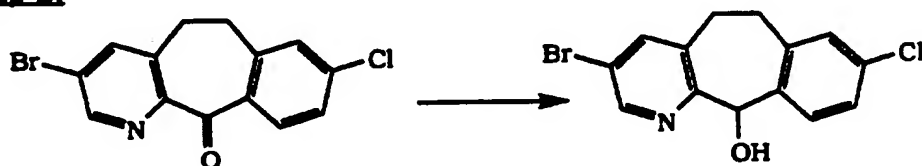
In the examples, MH^+ represents the molecular ion plus hydrogen of the molecule in the mass spectrum. Also, the following solvents and reagents are referred to herein by the abbreviations indicated: methanol (MeOH); ethyl acetate (EtOAc); and N,N-dimethylformamide (DMF).

25

PREPARATIVE EXAMPLE 1Step A:

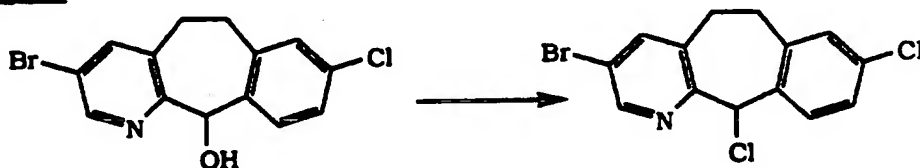
- Cool 50.0 g (20.5 mmol) of 8-Chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one to 0°C and slowly add 75 mL of sulfur monochloride over 20 minutes. Add 25 mL (48.59 mmol) of Br₂ over 15 minutes, then heat at 95°C for 20 hours. Add 12.5 mL (24.3 mmol) of Br₂ over 15 minutes and heat for 24 hours more. Cool the mixture and slowly add it to a mixture of CH₂Cl₂ and 1N NaOH (aqueous) at 0°C. Wash the organic phase with water dry over MgSO₄, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 500 mL of CH₂Cl₂, then 0.2%-5% (10% concentrated NH₄OH in MeOH)-CH₂Cl₂), then rechromatograph (silica gel, 3-8.5% EtOAc/hexane) to give 8.66 g of the product compound. Mass Spec.: MH⁺ = 322

Step B:

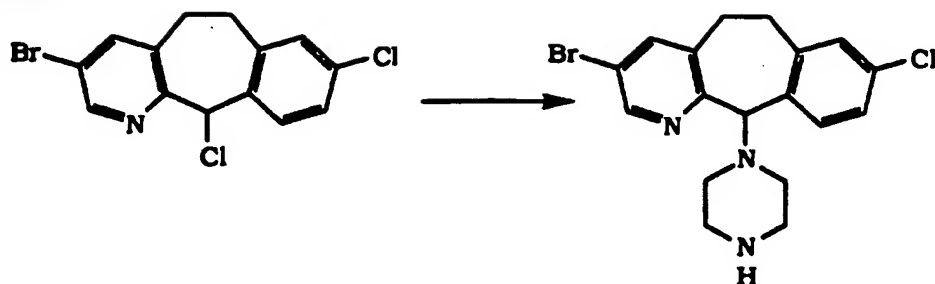


- Combine 6.84 g (21.2 mmol) of the product of Step A 160.5 mL of MeOH and treat with 1.1709 g of NaBH₄ as described in Preparative Example 7, Step A, of WO 95/10515, to give 5.93 g of the product compound. MH⁺ 326

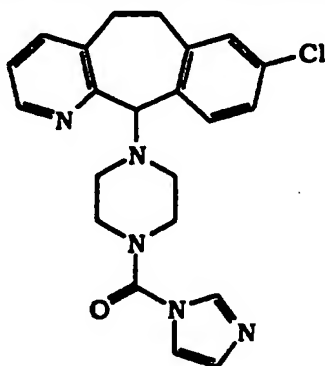
Step C:



- Combine 5.93 g (18.3 mmol) of the product of Step B and 116 mL of anhydrous toluene, cool to 0°C, and slowly add (dropwise) a solution of 2.465 g (33.9 mmol) of SOCl₂ in 23 mL of anhydrous toluene over a period of 0.5 hours. Stir at 0°C for 1.5 hours and at 0°-25°C for 2 hours, then work up as described in Preparative Example 7, Step B, of WO 95/10515, to give the product compound.

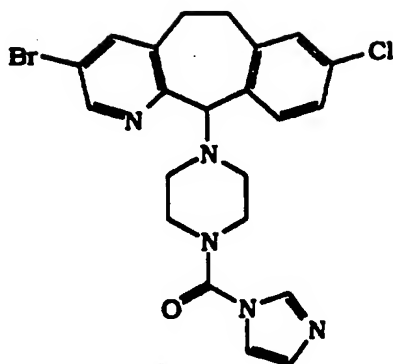
Step D:

React 18.3 mmol of the product of Step C with 9.94 g (91.5 mmol) of piperazine via the procedure described in Preparative Example 7, Step C, of WO 95/10515, to give 8.0 g of the title compound. Mass Spec.: $MH^+ = 394$

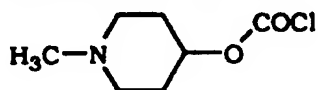
PREPARATIVE EXAMPLE 2

- 10 Combine 10 g (31.9 mmol) of the product of Preparative Example 7, Step C, of WO 95/10515, 100 mL of dry CH_2Cl_2 and slowly (dropwise) add the solution to a mixture of 5.17 g (31.9 mmol) of carbonyldiimidazole in 150 mL of dry CH_2Cl_2 over 0.75 hours. Stir at $0^\circ C$ for 2 hours, wash with water, dry over $MgSO_4$, and concentrate *in vacuo* to a residue.
- 15 Chromatograph (silica gel, 2% (10% conc. NH_4OH in $MeOH$)/ CH_2Cl_2) to give 8.71 g of the title compound. Mass Spec.: $MH^+ = 408.2$

Using the product of Preparative Example 1, Step D, and essentially the same procedure as described for Preparative Example 2, the following compound is prepared:

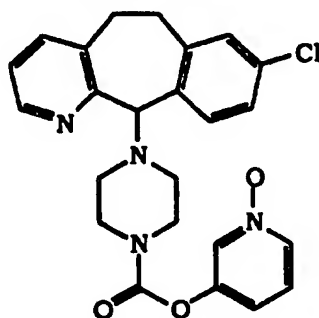


Preparative Example 2-A

Mass Spec.: $MH^+ = 488.2$ **PREPARATIVE EXAMPLE 3**

Combine 10 mL of dry CH_2Cl_2 and 914.6 mL (28.1 mmol) of a 1.93
 5 M solution of phosgene in toluene, cool to $0^\circ C$ and slowly add (dropwise)
 a solution of 0.6484 g (5.62 mmol) of 3-hydroxy-1-N-methylpiperidine,
 1.214 mL (15 mmol) of pyridine and 10 mL of dry CH_2Cl_2 , over 10 min.,
 then stir at 0° - $25^\circ C$ for 2 hours. Purge excess phosgene with N_2 then
 concentrate *in vacuo* to give the title compound.

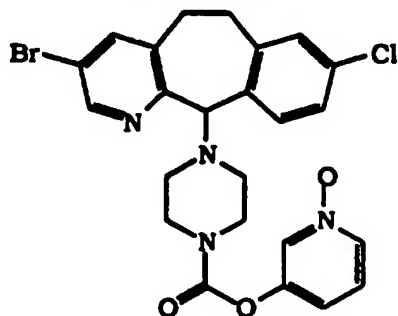
10

EXAMPLE 1

Combine 12 mL of dry CH_2Cl_2 and 12.58 mL (23.9 mmol) of a 28%
 solution of phosgene in toluene, cool to $0^\circ C$ under Ar atmosphere and
 15 slowly add (dropwise) a solution of 0.5 g (1.59 mmol) of the product of
 Preparative Example 7, Step C, of WO 95/10515, 0.515 mL (6.36 mmol) of
 pyridine and 12 mL of dry CH_2Cl_2 , over 0.75 hours, then warm the mixture
 to $12^\circ C$ over 0.5 hours. Purge excess phosgene with Ar then concentrate
in vacuo to a residue. Add 10 mL of DMF, 0.515 mL of pyridine and 0.885
 20 g (7.95 mmol) of 3-hydroxypyridine-1-N-oxide and stir at $25^\circ C$ for 18
 hours. Dilute with CH_2Cl_2 , wash with sat. $NaHCO_3$ (aqueous) and dry

over MgSO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give 0.186 g of the title compound. Mass Spec.: $\text{MH}^+ = 451.3$

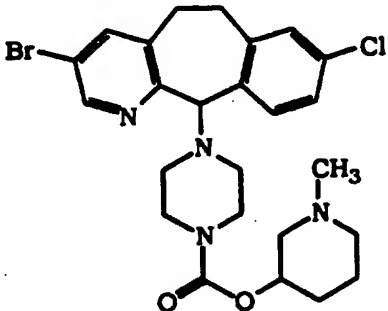
5

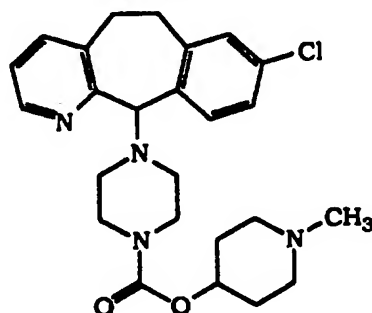
EXAMPLE 2

Combine 0.1 g (0.205 mmol) of the product of Preparative Example 2-A, 0.0463 g (0.205 mmol) of ZnBr_2 , 0.0913 g (0.822 mmol) of 3-hydroxypyridine-1-N-oxide and 3 mL of dry DMF, and heat the mixture at 90°C for 51 hours, then stir at 25°C for 19 hours. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give 0.0812 g of the title compound. Mass Spec.: $\text{MH}^+ = 531.1$

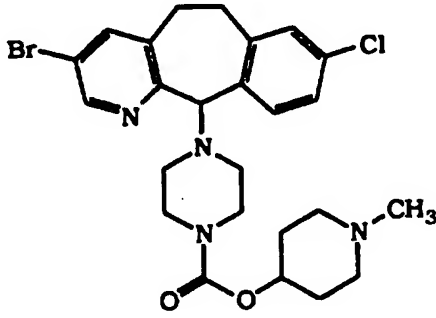
Using the starting compounds indicated and following essentially the same procedure as described for Example 2, the following compounds are obtained:

Starting Compound	Product Compound	Analytical Data
3-hydroxy-1-N-methylpiperidine and Preparative Example 2	<p>Example 2-A</p>	Mass Spec.: $\text{MH}^+ = 455.25$

3-hydroxy-1-N-methylpiperidine and Preparative Example 2-A	 Example 2-B	Mass Spec.: MH ⁺ = 533.15
---------------------------------------------------------------------	---------------------------------------------------------------------------------------------------	-----------------------------------------

EXAMPLE 3

- Combine 0.5 g (1.6 mmol) of the product of Preparative Example 7,
5 Step C, of WO 95/10515, 0.849 g (4.8 mmol) of the title compound of
Preparative Example 3, and 10 mL of 1:1 pyridine/CH₂Cl₂, and stir at 25°C
for 19 hours. Workup as described for Example 4, of WO 95/10515, and
chromatograph (silica gel, 3% (10% NH₄OH in MeOH)/CH₂Cl₂) to give
0.5231 g of the title compound. Mass Spec.: MH⁺ = 455.25
10 Using the starting compound indicated and following essentially the
same procedure as described for Example 3, the following compound is
obtained:

Starting Compound	Product Compound	Analytical Data
Preparative Example 1	 Example 3-A	Mass Spec.: MH ⁺ = 533.15

FPT IC₅₀ (inhibition of Farnesyl Protein Transferase by *in vitro* enzyme assays) and COS IC₅₀ (Cell-Based Assay) were determined using the methods described in WO 95/10515. The results are given in Table 1 below. Cell Mat Assays and *in vivo* anti-tumor studies could be
5 done by the methods described in WO 95/10515.

TABLE 1
FPT INHIBITION

COMPOUND	FPT IC ₅₀ (μM)	COS IC ₅₀ (μM)
(800.00) Example 1	0.01-10	-----
(801.00) Example 2	0.01-10	-----
(802.00) Example 3	10-100	-----
(803.00) Example 3-A	0.01-10	10-100
(804.00) Example 2-A	0.01-10	-----
(805.00) Example 2-B	0.01-10	-----

10

The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat and human brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC₅₀ <10
15 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT)--see Table 1.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets,
20 dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral
25 administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds,
30 allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

5 Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

10 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

15 The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

20 Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

25 The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

30 The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

35 The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is

oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

- 5 The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	<u>3</u>	<u>7</u>
Total		300	700

10

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes.

Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules.

- 15 Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B - Capsules

20

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	<u>7</u>	<u>7</u>
Total		253	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

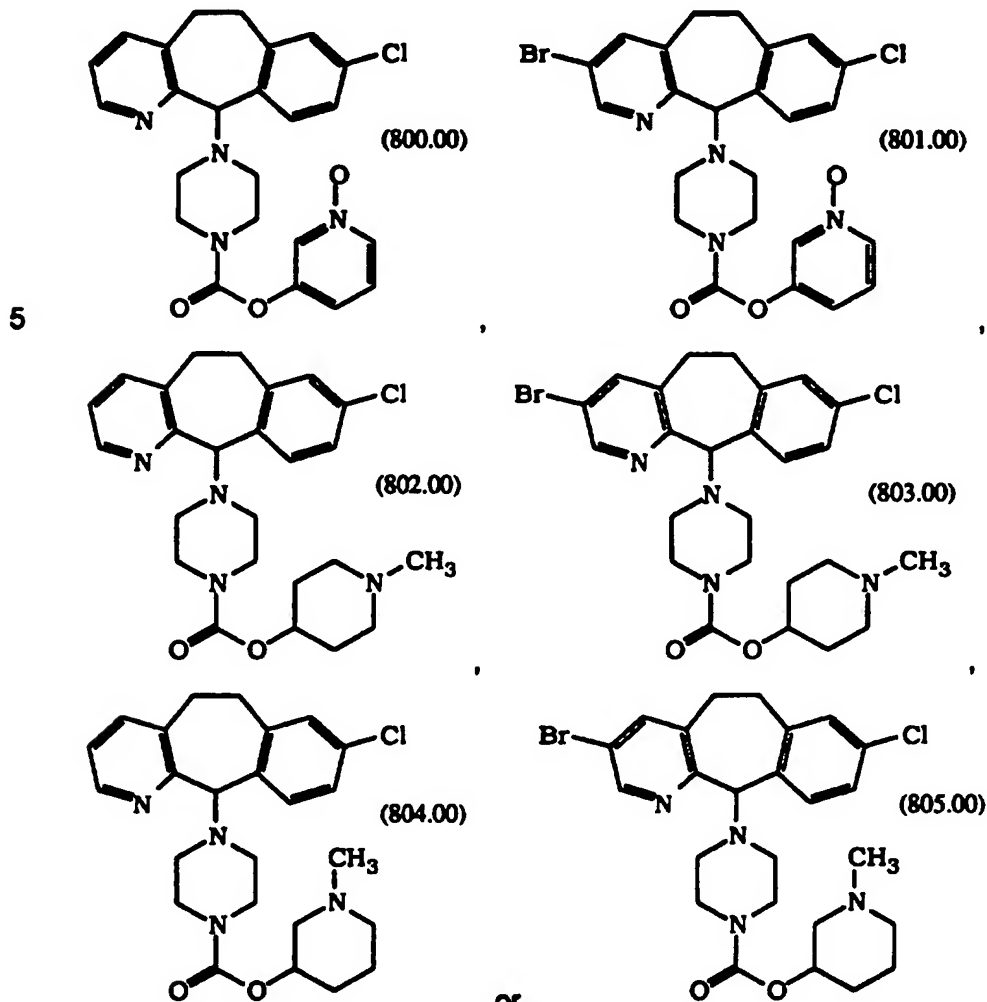
5

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art.

All such alternatives, modifications and variations are intended to fall
10 within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound selected from:



2. The method of Claim 1 wherein the cells inhibited are tumor cells expressing an activated Ras oncogene.

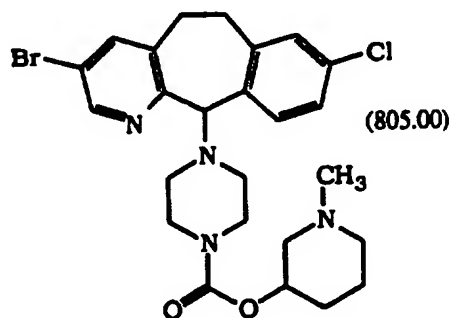
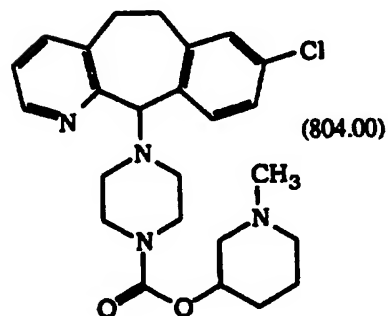
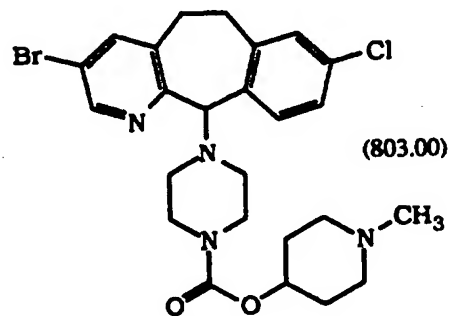
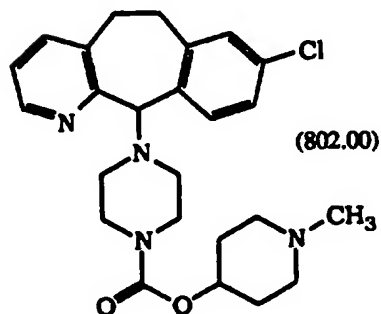
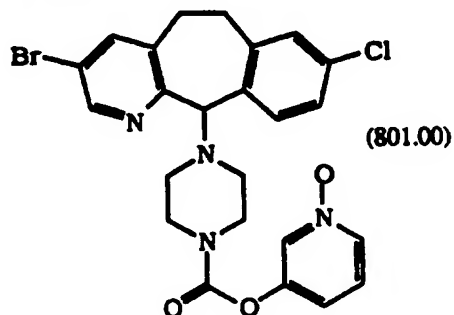
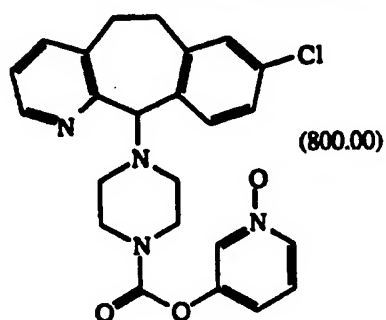
3. The method of Claim 2 wherein the cells inhibited are pancreatic tumor cells, lung cancer tumor cells, epidermal carcinoma tumor cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic cells, bladder carcinoma tumor cells or colon tumor cells.

4. The method of Claim 1 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of farnesyl protein transferase.

5. The method of Claim 1 wherein the inhibition is of tumor cells wherein Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

5

6. A compound selected from a compound of the formula:



,or

7. A pharmaceutical composition, for use in inhibiting the growth of abnormal cells, comprising a pharmaceutically acceptable carrier and an effective amount of a compound of Claim 6.

15

8. The use of a compound of Claim 6 for the manufacture of a medicament for use in inhibiting the growth of abnormal cells.

9. The use of a compound of Claim 6 in inhibiting the growth of abnormal cells

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/US 96/03312

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A,95 10616 (SCHERING CORP.) 20 April 1995 see page 137; example 201 see page 138; example 206 see page 186; example 352 see page 219; examples 185,225 see claim 1	1-9
X,P	--- WO,A,95 10515 (SCHERING) cited in the application see claims 1,5-7,9-11 see page 31, compound 600.00 see page 32, compound 608.00	1-9
A	--- WO,A,88 03138 (SCHERING) see page 40 see claim 1 --- -/-	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

20 August 1996

Date of mailing of the international search report

02.09.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Gerli, P

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 96/03312

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 089 496 (SCHERING) see claim 1	1-9
A	--- EP,A,0 396 083 (SCHERING) see page 72, line 20 - line 35 see page 21 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/03312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9510616	20-04-95	AU-B- 7937994	04-05-95
		CA-A- 2174116	20-04-95
		EP-A- 0723593	31-07-96
		GB-A- 2296717	10-07-96
		AU-B- 7856394	04-05-95
		CA-A- 2174115	20-04-95
		WO-A- 9510618	20-04-95
		EP-A- 0723592	31-07-96
		GB-A- 2297090	24-07-96
		AU-B- 7856294	04-05-95
		CA-A- 2174117	20-04-95
		WO-A- 9510617	20-04-95
		EP-A- 0723591	31-07-96
		GB-A- 2296243	26-06-96
WO-A-9510515	20-04-95	AU-B- 7930994	04-05-95
		CA-A- 2174105	20-04-95
		EP-A- 0723538	31-07-96
WO-A-8803138	05-05-88	US-A- 4826853	02-05-89
		AT-T- 116310	15-01-95
		AU-B- 7285991	30-05-91
		AU-B- 604285	13-12-90
		AU-B- 8336287	25-05-88
		CA-A- 1305147	14-07-92
		CA-A- 1321589	24-08-93
		DE-D- 3750929	09-02-95
		DE-T- 3750929	01-06-95
		EP-A- 0270818	15-06-88
		EP-A- 0330673	06-09-89
		EP-A- 0685476	06-12-95
		ES-T- 2068179	16-04-95
		FI-B- 96768	15-05-96
		JP-B- 6078316	05-10-94
		JP-T- 2500910	29-03-90
		OA-A- 9546	31-01-93
		US-A- 5089496	18-02-92
		US-A- 5438062	01-08-95
		ZA-A- 8708128	29-04-88

INTERNATIONAL SEARCH REPORT

In. .nation on patent family members

Internati Application No

PCT/US 96/03312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5089496	18-02-92	US-A- 4826853	02-05-89
		AT-T- 114650	15-12-94
		AU-B- 643946	02-12-93
		AU-B- 5642090	29-11-90
		CA-A- 2053903	02-11-90
		DE-D- 69014393	12-01-95
		DE-T- 69014393	01-06-95
		EP-A- 0396083	07-11-90
		EP-A- 0471750	26-02-92
		ES-T- 2064520	01-02-95
		IL-A- 94258	07-10-94
		JP-T- 4504724	20-08-92
		KR-B- 9509859	29-08-95
		OA-A- 9521	15-11-92
		WO-A- 9013548	15-11-90
		US-A- 5151423	29-09-92
		US-A- 5438062	01-08-95
		AT-T- 116310	15-01-95
		AU-B- 7285991	30-05-91
		AU-B- 604285	13-12-90
		AU-B- 8336287	25-05-88
		CA-A- 1305147	14-07-92
		CA-A- 1321589	24-08-93
		DE-D- 3750929	09-02-95
		DE-T- 3750929	01-06-95
		EP-A- 0270818	15-06-88
		EP-A- 0330673	06-09-89
		EP-A- 0685476	06-12-95
		ES-T- 2068179	16-04-95
		FI-B- 96768	15-05-96
		JP-B- 6078316	05-10-94
		JP-T- 2500910	29-03-90
		OA-A- 9546	31-01-93
		WO-A- 8803138	05-05-88
		ZA-A- 8708128	29-04-88

EP-A-396083	07-11-90	US-A- 5089496	18-02-92
		AT-T- 114650	15-12-94
		AU-B- 643946	02-12-93
		AU-B- 5642090	29-11-90

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/03312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-396083		CA-A- 2053903	02-11-90
		DE-D- 69014393	12-01-95
		DE-T- 69014393	01-06-95
		EP-A- 0471750	26-02-92
		ES-T- 2064520	01-02-95
		IL-A- 94258	07-10-94
		JP-T- 4504724	20-08-92
		KR-B- 9509859	29-08-95
		OA-A- 9521	15-11-92
		WO-A- 9013548	15-11-90
		US-A- 5151423	29-09-92
		US-A- 5438062	01-08-95

This Page Blank (uspto)